Xylenes (CASRN 1330-20-7)

view QuickView

IRIS List of IRIS Substances

Select a Substance go

Full IRIS Summary QuickView

MAIN CONTENTS

Reference Dose for Chronic Oral Exposure (RfD) go

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe* PDF format (113 Pages, 498 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to the IRIS Help page for instructions.

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Xylenes; CASRN 1330-20-7

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Xylenes

File First On-Line 09/30/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/21/2003
Inhalation RfC Assessment (I.B.)	on-line	02/21/2003
Carcinogenicity Assessment (II.)	on-line	02/21/2003

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Xylenes
CASRN -- 1330-20-7

183258

SUBSTANCE SUMMARY INDEX

Chronic Health Hazards for Non-Carcinogenic Effects
Reference Dose for Chronic Oral Exposure (RfD)
- Oral RfD Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/ Comments
- Confidence in the Oral RfD
- EPA Documentation and Review

Reference Concentration for Chronic Inhalation Exposure (RfC)
- Inhalation RfC Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/ Comments
- Confidence in the Inhalation RfC
- EPA Documentation and Review

Carcinogenicity Assessment for Lifetime Exposure
Evidence for Human Carcinogenicity
- Weight-of-Evidence Characterization
- Human Carcinogenicity Data
- Animal Carcinogenicity Data
- Supporting Data for Carcinogenicity

Last Revised -- 02/21/2003

The oral Reference Dose (RfD) is based on the assumption that thresholds generally exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The RfD in this updated assessment replaces a previous RfD value of 2 mg/kg-day. The previous and new RfD values are based on the same principal study (NTP, 1986). A database uncertainty factor (UF) was not considered in the derivation of the previous RfD.

The term xylenes refers to mixtures of the three xylene isomers (o-, m-, p-) and ethylbenzene. m-Xylene is commonly the predominant component (40–77%) in commercial preparations of xylenes (also referred to as mixed xylenes), with the other components each comprising roughly up to 20% of the mass. The use of xylenes as a solvent, in paints and coatings, and in gasoline is widespread. For the most part, studies cited in this assessment are conducted on mixed xylenes. Results from studies comparing the toxicity of individual xylene isomers indicate that differences, when they occur, are specific to the endpoint under consideration (see Section 4.4.3 of the Toxicological Review for more information).

Quantitative Estimate of Carcinogenic Risk from Oral Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts

- Bibliography
- Revision History
- Synonyms

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weight, increased mortality	NOAEL: 250 mg/kg-day (179 mg/kg-day)*	1000	1	0.2 mg/kg-day
Chronic F344/N rat study Oral gavage exposure	LOAEL: 500 mg/kg-day			
(NTP, 1986)				

*Conversion Factors and Assumptions -- 250 mg/kg-day x 5 days/7 days = 179 mg/kg-day.

__I.A.2. Principal and Supporting Studies (Oral RfD)

The National Toxicology Program's 2-year study in rats was selected as the principal study and the subchronic toxicity studies in rats by Wolfe (1988a, b) as supporting studies. In the NTP (1986) study, groups of 50 male and 50 female Fischer 344 rats and 50 male and 50 female B6C3F1 mice were administered mixed xylenes (60% m-xylene, 13.6% p-xylene, 9.1% o-xylene, 17.0% ethylbenzene) in corn oil by gavage at doses of 0, 250, or 500 mg/kg-day (rats) and 0, 500, or 1000 mg/kg-day (mice) for 5 days per week for 103 weeks. Necropsy and histologic examinations were performed on all animals. Tissues were examined for gross lesions and masses. The tissues examined included mandibular lymph nodes, salivary gland, femur (including marrow), thyroid gland, parathyroids, small intestine, colon, liver, prostate/testis or ovaries/uterus, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, skin, lungs and mainstem bronchi, kidneys, adrenal glands, urinary bladder,

pituitary gland, eyes (if grossly abnormal), and mammary gland. Hematology and clinical chemistry analyses were not conducted.

Effects of exposure in rats were limited to decreased body weight and decreased survival in high-dose (500 mg/kg-day) males. Mean body weights were 5–8% lower in high-dose male rats than in controls from week 59 to week 97, with body weights at 103 weeks being 4% less in high-dose males than in controls (statistical significance not reported). Male rat survival rates after 103 weeks showed a dose-related decrease (36/50, 25/50, and 20/50 for the control, low-, and high-dose males, respectively). A life-table trend test for decreased survival incidence with increasing dose was statistically significant (p=0.033). Pair-wise comparisons with control survival incidence indicated that only the high-dose male rat incidence was significantly decreased (p=0.04). A number of the deaths were attributed to gavage error (3/50, 8/50, and 11/50, respectively, for the control, low-, and high-dose groups). The authors did not record observations of rat behavior during dosing. Based on the available observations, the incidence of treatment-related deaths demonstrated a dose-related increase (11/50, 17/50, and 19/50, respectively [22%, 34%, and 38%]). The LOAEL is 500 mg/kg-day and the NOAEL is 250 mg/kg-day for decreased body weight and decreased survival. There was no evidence of carcinogenicity in male or female rats exposed to doses up to 500 mg/kg-day.

In mice, the only treatment-related effect observed was hyperactivity, which occurred in all high-dose mice of each sex, 5–30 minutes after dosing. This effect was observed consistently beginning at week 4, and it continued until study termination at 103 weeks. The LOAEL is 1000 mg/kg-day and the NOAEL is 500 mg/kg-day for hyperactivity.

In a study by Wolfe (1988a), groups of 20 male and 20 female Sprague-Dawley rats were administered m-xylene (99% purity) by gavage in corn oil at doses of 0, 100, 200, or 800 mg/kg-day for 90 consecutive days. Survival incidences were 20/20, 17/20, 15/20, and 18/20, respectively, for males, and 20/20, 20/20, 16/20, and 16/20 for females. Mortality in the mid-dose males and mid- and high-dose females attained statistical significance ($p \leq 0.05$), but a significant trend was observed only in females. Mottled lungs and a failure of the lungs to collapse were observed in all mid- and high-dose animals that died early and in 2/3 of the low-dose males that died early but was not evident in any of the animals that survived to study termination. Histopathologic examination of the lungs from animals that died before study termination revealed foreign material in the alveoli in all but one animal. Therefore, these deaths were attributed to vehicle and/or compound aspiration.

Clinical signs present throughout the study were limited to high levels of salivation prior to dosing in high-dose males and females. Body weight gains over the entire study period were decreased ($p \leq 0.05$) in mid- and high-dose males (89% and 75% of controls', respectively) and high-dose females (85% of controls'). Food consumption was likewise decreased ($p \leq 0.05$) in high-dose males during weeks 1–5 (90% of control levels) and in mid- and high-dose males during weeks 6–9 (92% of control levels for both groups). A thorough histologic examination revealed no other abnormal findings. Other effects noted were not definitively related to treatment and/or were not biologically significant. The NOAEL and LOAEL are identified as 200 and 800 mg/kg-day, respectively, based on decreased body weight.

In a second study by Wolfe (1988b), groups of 20 male and 20 female Sprague-Dawley rats were administered p-xylene (99% purity) by gavage in corn oil at doses of 0, 100, 200, or 800 mg/kg-day for 90 consecutive days. Survival incidences were 20/20, 19/20, 17/20, and 16/20, respectively, for males, and 20/20, 18/20, 18/20, and 17/20 for females. Mortality in high-dose males attained statistical significance, and a statistically significant trend was present in the male groups. As in the Wolfe (1988a) study, mottled lungs and/or a failure of the lungs to collapse was observed in nearly all treated animals that died early but was not evident in any of the animals that

survived to study termination. It was determined that most of the unscheduled deaths were the result of test material aspiration, as indicated by the presence of intra-alveolar foreign material in the lungs that was generally associated with pulmonary congestion.

Treatment-related clinical signs were limited to increased salivation occurring just prior to dosing that was resolved by 1-hour post-dosing in both high-dose males and females. Body weight gains at 13 weeks were slightly reduced (89% of control levels, not statistically significant) in high-dose males and females, and high-dose females had significantly increased food consumption for weeks 10–13 (110%). No treatment-related effects were observed in hematology or clinical chemistry parameters, ophthalmologic examination, or organ weights. Histopathology revealed no abnormal findings in any tissue or organ. The NOAEL and LOAEL are identified as 200 and 800 mg/kg-day, respectively, based on early mortality in male rats that showed signs of test material aspiration into the lungs.

The NTP (1986) 2-year study in rats was selected as the principal study for the derivation of the RfD for xylenes because it is the only oral animal study of chronic duration, and some effects (decreased body weight and possible increased mortality) were evident at doses lower than those for effects seen in other studies. The body weight decrease (5–8% of controls') is considered to be of marginal biological significance, but there was a statistically significant trend for decreased survival in male rats with increasing exposure levels, and survival in the high-dose males was statistically significantly decreased when compared with controls. Given the possibility of treatment-related frank toxicity, it is not considered prudent to discount the only other observed effect, i.e., decreased body weight. Thus, the highest dose in the study, 500 mg/kg-day, is considered a LOAEL for changes in body weight and mortality.

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 1000

A UF of 10 was applied to account for laboratory animal-to-human interspecies differences. No information is available to support a change from default.

A UF of 10 was applied for intraspecies uncertainty to account for human variability and sensitive populations. This factor accounts for humans who may be more sensitive than the general population to exposure to xylenes.

A UF of 10 was used to account for database uncertainty. The available oral database for xylenes includes chronic and subchronic gavage toxicity studies in mice and rats and a developmental toxicity study. None of these studies indicate that additional data would result in a lower RfD. However, the database lacks adequate studies of the oral neurotoxicity of xylenes as well as multigenerational reproductive toxicity and developmental neurotoxicity studies. Given the identification of neurological impairment as a critical health hazard from inhalation exposure to xylenes, the lack of comprehensive neurotoxicity testing following chronic oral exposure is of particular concern. It should be noted that transient neurotoxic effects (e.g., lethargy, tremors and unsteadiness) were reported in mice following oral exposure to xylenes for 13 weeks (NTP, 1986). There are no toxicokinetic data identifying oral dose levels at which first-pass hepatic metabolism of xylenes becomes saturated in animals or humans; such data could decrease uncertainty regarding whether neurological impairment may occur at dose levels below those causing body weight decreases and mortality in rats. It is uncertain whether the availability of comprehensive oral neurotoxicity data would result in a lower RfD.

An additional uncertainty associated with the oral database is that the majority of studies examined mixed xylenes, which are known to contain ethylbenzene. The IRIS

assessment for ethylbenzene (U.S. EPA, 2002a), which was entered on the database in 1987, cites effects on liver and kidney as the most sensitive endpoints following oral exposure. As discussed below, effects on the liver and kidney have been reported following oral exposure to mixed xylenes, but the most sensitive effect reported in animal bioassays is decreased body weight and increased mortality, as identified by the principal study (NTP, 1986). However, because the mechanism behind the critical effect has not been clearly elucidated, a possible contribution of ethylbenzene to the toxicity of mixed xylenes cannot be entirely eliminated. Additional studies comparing the toxicity of mixed xylenes with that of the individual isomers would better inform the database.

The RfD is based on a NOAEL from a chronic study, which obviates the need for a UF due to LOAEL to NOAEL extrapolation or subchronic extrapolation.

MF = 1

__I.A.4. Additional Studies/Comments (Oral RfD)

In a NTP (1986) study, groups of 10 male and 10 female Fischer 344 rats were administered mixed xylenes (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, 9.1% o-xylene) in corn oil by gavage at doses of 0, 62.5, 125, 250, 500, or 1000 mg/kg-day for 5 days per week for 13 weeks. At termination of the study, necropsy was performed on all animals and comprehensive histologic examinations were performed on vehicle and high-dose group animals. High-dose males and females gained 15% and 8% less body weight, respectively, than did controls, with final body weights being 89% and 97%, respectively, of those of controls (statistical significance not reported). No signs of toxicity or treatment-related gross or microscopic pathologic lesions were observed. The LOAEL is 1000 mg/kg-day and the NOAEL is 500 mg/kg-day based on decreased body weight in male rats without tissue lesions.

In the same study, male and female B6C3F$_1$ mice were treated with mixed xylenes. Groups of 10 mice of each sex were administered 0, 125, 250, 500, 1000, and 2000 mg/kg-day in corn oil by gavage for 5 days per week for 13 weeks. Two female mice in the high-dose group died prematurely, although gavage error could not be ruled out as the cause. At 2000 mg/kg-day, starting 5–10 minutes after dosing and lasting for 15–60 minutes, the animals exhibited lethargy, short and shallow breathing, unsteadiness, tremors, and paresis. In the high-dose group, mean body weight was 7% lower for males and 17% lower for females than in the vehicle control. Although not stated explicitly, the text implies that this was a common finding among the animals dosed at this level. No treatment-related gross or microscopic pathologic lesions were seen in this study. The NOAEL is 1000 mg/kg-day and the LOAEL is 2000 mg/kg-day for transient signs of nervous system depression in mice without tissue lesions.

In a study by Condie et al. (1988) groups of 10 male and 10 female Sprague-Dawley rats were administered mixed xylenes (17.6% o-xylene, 62.3% m-xylene and p-xylene [which coeluted], 20% ethyl benzene) by gavage in corn oil for 90 consecutive days at doses of 0, 150, 750, or 1500 mg/kg-day. Effects of exposure included decreased body weights in high-dose males (94% of controls'), dose-related increased liver weights and liver-to-body weight ratios in all exposed groups of males (8, 18, and 29% increase in absolute weight above controls' in the low-, mid-, and high-dose animals, respectively) and in mid- and high-dose females (14 and 30%, respectively), and increased kidney weights and kidney-to-body weight ratios in mid- and high-dose males (16 and 19% increase in absolute weight relative to controls', respectively) and high-dose females (18% increase in absolute weight relative to controls). The authors postulated that the modest increases in aspartate aminotransferase seen in high-dose females and increases in alanine aminotransferase in high-dose males and in mid- and high-dose females, combined with the lack of significant histopathologic findings in the liver, suggest that the

enlargement of the liver was an adaptation response to xylenes treatment rather than an adverse toxicological effect.

Hematology analysis revealed a mild polycythemia and leukocytosis in the high-dose males and females in the absence of any observable changes in the health of the rats. Microscopic evaluation of the kidneys revealed a dose-related increase in hyaline droplet formation in male rats (0/9, 3/9, 5/10, 8/10, respectively) and a dose-related increase in the early appearance of minimal chronic nephropathy in female rats (1/10, 3/10, 6/10, 7/10, respectively). Compared with controls, the incidence of minimal nephropathy was statistically significantly elevated ($p<0.05$) in the 750 and 1500 mg/kg-day female groups but not in the 150 mg/kg-day group (Fishers exact test performed by Syracuse Research Corporation). The hyaline droplet formation in male rats was assumed by the authors to be related to male rat-specific α-2μ-globulin accumulation and not to be relevant to humans. The LOAEL is 750 mg/kg-day, based on increased kidney weights and early appearance of mild nephropathy in female rats, and the NOAEL is 150 mg/kg-day.

Kidney effects were not found in the NTP (1986) bioassay with Fisher 344/N rats or B6C3F1 mice exposed to xylenes for 13 weeks or 2 years. Likewise, no nephropathy was reported in a nephrotoxicity screening assay in male Fischer 344/N rats exposed to 2000 mg/kg m-xylene for 5 days per week for 4 weeks (Borriston Laboratories, Inc., 1983). In addition, no kidney effects were found in Sprague-Dawley rats exposed for 90 days to m-xylene or p-xylene at doses as high as 800 mg/kg-day (Wolfe et al., 1988a, b). Thus, the available data do not consistently identify the kidney as a sensitive target of xylenes in animals. Likewise, the available data do not consistently identify the liver as a sensitive target of xylenes in animals (NTP, 1986; Wolfe et al., 1988a, b; Condie et al., 1988).

A developmental toxicity study in CD-1 mice (Nawrot and Staples, 1980) indicates that developmental effects may occur following exposure to xylenes. However, the study was reported as an abstract with incomplete documentation of exposure protocols and results; it does not identify reliable NOAELs and LOAELs for maternal and developmental toxicity. Nevertheless, information in the abstract indicates that exposure on gestation days 6–15 to daily doses of o-, m-, or p-xylene at 1935 or 2580 mg/kg-day—but not at 774 mg/kg-day—resulted in overt maternal toxicity and increased incidences of cleft palate in the fetuses.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

__I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Medium
RfD -- Medium

Confidence in the principal study is medium. The study was a 2-year toxicology and carcinogenesis assay that evaluated the critical endpoint for RfD derivation (body weight and mortality) and included comprehensive histologic examination of tissues for nonneoplastic and neoplastic lesions. Some gavage errors occurred during the study, limiting the confidence assessment to medium. Confidence in the oral exposure database is medium because the database contains chronic animal studies in two species (rats and mice), numerous subchronic studies, and an evaluation of the developmental effects of oral xylenes, but it is lacking oral neurotoxicity studies as well as multigenerational reproductive toxicity and developmental neurotoxicity studies. Medium confidence in the RfD follows.

For more detail on Characterization of Hazard and Dose Response, exit to the

toxicological review, Section 6 (PDF).

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document – U.S. EPA, 2002a

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA (2002a). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***

Agency Consensus Date – 01/30/2003

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

Back to top

_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 02/21/2003

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

As noted in Section I.A. of this file, xylenes refers to mixtures of all three xylene isomers and ethylbenzene. The inhalation RfC for xylenes presented herein is based on a principal study (Korsak et al., 1994) in which rats were exposed by inhalation to m-xylene. There is some uncertainty associated with selecting a principal study for xylenes that involved exposure to m-xylene alone, but this isomer is generally predominant in commercial mixtures. In addition, although there are no studies comparing xylene isomers in affecting critical neurological endpoints following subchronic or chronic inhalation exposure, the potencies of individual xylene isomers were similar in affecting neurobehavior, as shown in a study of rats following acute exposures (Moser et al., 1985) (see Section 4.4.3 of the Toxicological Review for

more information).

No inhalation RfC for xylenes has previously been on IRIS.

__I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Impaired motor coordination (decreased rotarod performance)	NOAEL: 50 ppm $NOAEL_{(HEC)}$: 39 mg/m^3	300	1	0.1 mg/m^3
Subchronic inhalation study in male rats	LOAEL: 100 ppm $LOAEL_{(HEC)}$: 78 mg/m^3			

(Korsak et al., 1994)

*Conversion Factors and Assumptions - MW = 106.17. Assuming 25C and 760 mmHg, NOAEL(mg/m^3) = 50 ppm x 106.17/24.45 = 217 mg/m^3. $NOAEL_{[ADJ]}$ = 217 mg/m^3 x 6 hrs/day x 5 days/7 days = 39 mg/m^3. The $NOAEL^*_{[HEC]}$ was calculated for extrarespiratory effects of a Category 3 gas (U.S. EPA, 1994). Blood/gas partition coefficients: $H(b/g)_{rat}$ = 46.0; $H(b/g)_{human}$=26.4 (Tardif et al., 1995). $(H_{b/g})_{rat}/(H_{b/g})_{human}$ =1.7; value of 1 is used when the ratio is >1 (U.S. EPA, 1994). $NOAEL^*_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g})_{rat}/(H_{b/g})_{human}$ = 39 mg/m^3.

__I.B.2. Principal and Supporting Studies (Inhalation RfC)

Korsak et al. (1992) exposed groups of 12 male Wistar rats to toluene, m-xylene, or a 1:1 mixture for 6 hours per day, 5 days per week at a concentration of 0 or100 ppm for 6 months or 1000 ppm for 3 months. Rotarod performance and spontaneous motor activity were assayed 24 hours after termination of the exposure periods. The rotarod test was used as a measure of motor coordination disturbances from exposure to m-xylene. The rotarod test involves placing the subject animals on a rotating rod and evaluating their ability to remain on the rod for a period of 2 minutes. The animals were trained to perform the task, exposed to chemical or control gas, and evaluated at defined intervals. By the time interval after exposure, considerable proportions of absorbed xylenes are expected to have been eliminated from the body (see Section 3.4 and Appendix B of the Toxicological Review).

Body weights and weights of seven organs were measured; only data for animals sacrificed after 3 months of exposure was reported (controls and 1000 ppm rats). At 3 and 6 months, blood samples were collected 24 hours after termination of exposure for measurement of serum chemistry variables (e.g., alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, alkaline phosphatase, and total protein) and hematologic variables (erythrocyte counts, hemoglobin concentration, hematocrit, leukocyte count, and differential leukocyte counts). Serum chemistry and hematologic results were reported only for rats exposed to 1000 ppm for 3 months. Statistical evaluations (using a p=0.05 level of significance) of collected data included analysis of variance, Dunnet's test, and Fishers exact test.

Rats exposed to m-xylene alone exhibited statistically significantly decreased rotarod performance and decreased spontaneous activity, as measured 24 hours after termination of the exposures, when compared with controls. The percentages of failures in the rotarod test were roughly 60% in rats exposed to 1000 ppm for 3 months, 35% in rats exposed to 100 ppm for 6 months, and 0% for controls at either time period. The mean spontaneous motor activity in rats exposed to 100 ppm for 6

months was about 400 movements per hour, compared with about 800 movements per hour for controls. Spontaneous motor activity data for rats exposed to 1000 ppm m-xylene for 3 months were not presented in the report. No statistically significant exposure-related changes in body weight, absolute or relative organ weights, or clinical chemistry or hematology variables were noted in rats exposed to 1000 ppm m-xylene for 3 months, with the exception of decreased differential counts (percentage of white blood cells counted) of lymphocytes (45.5 ± 9.5 vs. 60.8 ± 6 .4 for controls; 25% decrease) and increased counts of monocytes (16.3 ± 8.9 vs. 8.3 ± 4.2 for controls; 96% increase). Total counts of white blood cells (in units of cells per mm^3 of blood), however, were not statistically significantly changed by exposure. The LOAEL is 100 ppm, based on decreased rotarod performance and decreased spontaneous motor activity. No NOAEL was identified.

In a second study, Korsak et al. (1994) exposed groups of 12 male Wistar rats by inhalation to 0, 50, or 100 ppm m-xylene or n-butyl alcohol or a 1:1 mixture (purity of chemicals not provided) for 6 hours per day, 5 days per week, for 3 months and evaluated similar endpoints as in the earlier study (Korsak et al., 1992). Blood for clinical biochemistry and hematologic analysis was collected 24 hours after termination of exposure. The report does not specify the timing of the neurologic examinations; however, given that the 1994 study was conducted by the same group of investigators as the 1992 study and that one of the tests (rotarod performance) was the same in both studies, it appears reasonable to assume that the tests were administered 24 hours after termination of exposure. Statistical evaluations (using a p=0.05 level of significance) of the collected data included analysis of variance, Dunnet's test, and Fishers exact test.

No statistically significant exposure-related changes were noted in body weight gain, absolute or relative organ weights, hepatic activities of microsomal monooxygenases, lipid peroxidation, or levels of triglycerides in the liver. Statistically significant decreases in erythrocyte number were seen in animals exposed to 50 ppm (93% of controls') or 100 ppm (80.5% of controls') of m-xylene alone. Similarly, decreased levels of hemoglobin were reported in both groups (92% of controls' for both groups). At 100 ppm, a statistically significant increase in leukocyte number (35% increase over controls') was reported. Exposure to 50 or 100 ppm m-xylene alone also resulted in decreased rotarod performance starting at 1 month of exposure, which remained at the same level until the end of the 3-month exposure. Decreases were statistically significant in the 100 ppm group when compared with the controls. The results were presented in graphical form; the actual numerical data are not provided. The decreases in performance were roughly 8% and 33% for the 50 and 100 ppm groups, respectively, versus 0% for the controls.

Sensitivity to pain was assessed using the hot plate behavior test, in which the animals are placed on a hot (54°C) surface and the time interval between being placed on the plate and licking of the paws is measured. Rats exposed to 50 or 100 ppm m-xylene alone had statistically significantly increased sensitivity to pain at the end of the 3-month exposure (latency of the paw-lick response was 8.7 and 8.6 seconds, respectively, vs. 12.2 seconds for the controls). The LOAEL is 100 ppm, based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test, and the NOAEL is 50 ppm.

To evaluate whether xylenes influence aging of the central nervous system or induces persistent changes in radial maze performance, Gralewicz et al. (1995) exposed 8-month-old, male LOD-Wistar rats (20 per dose level) to air containing 0, 100, or 1000 ppm "pure" m-xylene (exact purity not provided) for 6 hours per day, 5 days per week, for 3 months. One-hour electroencephalograph (EEG) recordings were performed on days 28 and 56 of exposure and on days 14, 28, 56, and 84 after exposure. The number and duration of spontaneous neocortical spike and wave discharges (SWD) from the EEG were taken as electrophysiological indices of the biological age of the brain. As rats age, SWDs increase in number and become longer. Because of large interindividual variation in number and duration of SWDs

within each group, these variables were normalized to a percentage of the initial values. Exposed rats were not subjected to the daily exposure protocol when EEG recordings were made on days 28 and 56 during the exposure period. Tests of spatial learning in an 8-arm radial maze were also conducted for a 2-week period starting from day 70 after exposure to day 83.

During the first adaptation stage of the test (five consecutive daily training periods), rats were familiarized with the maze. The second stage (five consecutive daily trials) measured effectiveness of finding water in the maze (e.g., duration of trial, number of entries into the arms, number of omission and preservation errors). One-way or two-way parametric analysis of variance was applied to the collected data, and effects were regarded as statistically significant at $p<0.05$. Body weights were also measured during and after the exposure period at various intervals, but statistically significant differences were not found among the groups.

The analysis of variance indicated no group effect on the normalized number and cumulative-duration SWD variables. However, a statistically significant group x successive recording period effect was indicated. In control rats, these variables were increased to a statistically significant degree, compared with those of the exposed groups, only on day 84 after exposure. The mean cumulative SWD duration (expressed in percentage) on day 84 was about 300 for the control compared with means of about 150 in each of the exposed groups. The authors hypothesized that these exposure-related changes in the spontaneous, age-related changes in cortical SWD activity may be related to cortical excitability or to an increase in catecholaminergic transmissions.

Unlike the controls, rats exposed to 100 or 1000 ppm m-xylene did not exhibit a statistically significant shortening of the time needed to complete a trial in the radial maze with successive daily trials. These results indicate a learning deficit in the exposed rats. For example, on the fifth consecutive trial, the mean trial durations in each of the exposed groups were about 240–250 seconds, compared with a mean of about 150 seconds for the control group. In addition, the exposed groups did not exhibit the statistically significant decrease in omission errors with successive days in the radial arm maze test that was exhibited by the control group (number of arms in the maze omitted during a 5-minute period when the rats explored the maze). The mean number of omission errors in control rats showed a progressive decrease from about 2.75 on the first trial to 0 on the fourth and fifth successive trials. In contrast, the means on the fifth consecutive trial were about 1.5 and 2.5 for the 100 ppm and 1000 ppm groups, respectively. The lowest exposure level in this study, 100 ppm, is designated as a LOAEL for deficits in radial maze performance.

Gralewicz and Wiaderna (2001) exposed groups of male Wistar rats (10–11 animals/group) to 0 or 100 ppm of m-xylene for 6 hours per day, 5 days per week for 4 weeks. Behavioral testing was performed at various intervals before (radial maze and open-field evaluations) and after exposure (radial maze [days 14–18], open-field activity [day 25], passive avoidance [days 39–48], hot plate test [days 50–51], and active avoidance [days 54–60]). The radial maze and hot plate test protocols are described in previous studies from this group (Gralewicz and Wiaderna, 1995; Korsak et al., 1992).

In the open-field activity test, animals were placed in a 100 cm x 100 cm arena that was surrounded by 20 cm high walls and divided into 49 equal squares. The number of square borders crossed (locomotor activity), number of rearings (exploratory activity), and number of grooming episodes were recorded. In the passive avoidance test, animals were placed on a platform above the floor of the cage, and the time until the animal stepped off the platform was recorded in a series of six trials. In the first two trials, the animals were allowed to explore the cage for 60 seconds after stepping down; in the third trial, the animals received a series of footshocks after stepping off the platform. In trials 4, 5, and 6 the animals received no shocks and were allowed to

stay on the floor for 1 minute after stepping off the platform. In the active avoidance test, animals were trained to avoid an electric footshock by moving from one compartment of the cage to another when a sound is played. After successfully displaying avoidance behavior in four of five trials, the animals were considered to be trained. Post-exposure evaluations determined the frequency of avoidance behavior in response to the same stimulus.

No differences between control and exposed rats were seen in radial maze parameters (number of arm entries, arms omitted, or arms entered multiple times) either before exposure (7 days prior to exposure) or at 14–18 days after the termination of exposure. Similarly, no differences in open-field activity were seen between groups examined on day 8 prior to exposure or day 25 postexposure or in active avoidance (number of trials to avoidance criterion), examined on days 54 and 60 post-exposure. Xylene-exposed rats showed a significantly shorter step-down time (trial 6 only; no difference in trials 1–5) in the passive avoidance test (examined on days 39–48 postexposure) and a significantly greater paw-lick latency in the hot plate behavior test (examined on days 50–51 postexposure), identifying 100 ppm as a LOAEL for neurobehavioral effects.

Because available human data are insufficient for deriving an RfC and chronic animal inhalation data are lacking, the subchronic study of Korsak et al. (1994) was selected as the principal study and Korsak et al. (1992), Gralewicz et al. (1995), and Gralewicz and Wiaderna (2001) as the supporting studies. Neurological effects (impaired motor coordination) are selected as the critical effect for deriving the RfC. Two neurological endpoints were evaluated in this study. Rotarod performance was statistically significantly decreased (33% from controls') at 100 ppm, and a statistically significant decreased sensitivity to pain was observed at 50 and 100 ppm (8.6 and 8.7 seconds, respectively, vs. 12.2 seconds for controls; measurements made 24 hours postexposure). Gralewicz and Wiaderna (2001) also measured the effect of m-xylene exposure (6 hrs/day, 5 days/wk for 4 weeks; neurological endpoints measured postexposure day 50) on pain sensitivity. In this study, a statistically significant increase in pain sensitivity (35 seconds vs. 10 seconds in control) was found at the 100 ppm dose, the lowest dose tested. The variation in the response to m-xylene in these two studies decreases the confidence in using the pain sensitivity endpoint as the critical effect.

A number of statistically significant neurological effects have been noted in male rats at a dose of 100 ppm m-xylene in other supporting studies: decreased rotarod performance and spontaneous movement activity following exposure for 6 hours per day, 5 days per week for 6 months (Korsak et al., 1992), decreased radial maze performance following exposure for 6 hours per day, 5 days per week for 3 months (Gralewicz et al., 1995); and shortened step-down time in the passive avoidance test following exposure for 6 hours per day, 5 days per week for 4 weeks. All studies measured neurological endpoints 24 hours postexposure with the exception of Gralewicz and Wiaderna (2001), which measured effects at postexposure day 50. For these reasons, a NOAEL of 50 ppm and a LOAEL of 100 ppm is identified for neurological effects (impaired motor coordination).

The principal study (Korsak et al., 1994) reported no statistically significant exposure-related changes in body weight gain, absolute or relative organ weights, hepatic activities of monoxygenases or lipid peroxidation, or levels of triglycerides in the liver. Compared with controls, exposed rats showed statistically significant changes in red blood cell counts (7–20% decreased), hemoglobin levels (-8% decreased), and white blood cell counts (35% increased). Effects in red blood cell counts and hemoglobin levels were observed at 50 ppm. However, these changes were not observed in another study from the same laboratory (Korsak et al.,1992) in rats exposed to 1000 ppm m-xylene. Furthermore, effects on erythrocytes were not found at concentrations of 78–810 ppm in other studies (Carpenter et al., 1975; Jenkins et al., 1970).

__I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 300

A UF of 3 was applied to account for laboratory animal-to-human interspecies differences. A factor of 3 was applied because default $NOAEL_{[HEC]}$ dosimetric adjustments were used to calculate a human equivalent concentration (HEC), reducing the uncertainty involved with the extrapolation from the results of an animal study to a human exposure scenario (i.e., the toxicokinetic portion of the UF is 1; the toxicodynamic portion of the UF is 3).

A uncertainty factor of 10 was applied for intraspecies uncertainty to account for human variability and sensitive populations. The degree of human variance in abilities to absorb or dispose of xylenes is unknown, as is the degree of human variance in responding to xylenes neurotoxicity. Results from developmental toxicity studies of rats exposed by inhalation during gestation indicate that adverse developmental effects occur only at higher doses than chronic doses producing the critical effects observed in adult male rats in the principal and supporting studies, suggesting that the developing fetus is not at special risk from low-level exposure to xylenes. However, as with oral exposure, the effects of inhaled xylenes in other potentially sensitive populations such as newborns or young children or animals have not been assessed.

A UF of 3 was applied for extrapolation from subchronic to chronic duration. A factor of 10 was not used because the changes in rotarod performance did not increase with time from 1 to 3 months and were similar to those described in a separate study of 6-months duration (Korsak et al., 1992).

A UF of 3 was applied for uncertainties in the database. The inhalation database includes some human studies, subchronic studies in rats and dogs, neurotoxicity studies, a one-generation reproductive toxicity study, developmental toxicity studies, and developmental neurotoxicity studies. Although the available developmental toxicity studies are confounded by a lack of litter incidence reporting, the data reported for fetal incidences do not indicate effects at levels lower than that found to induce neurologic impairment in several endpoints in male rats. The database is lacking a two-generation reproductive toxicity study.

MF = 1

__I.B.4. Additional Studies/Comments (Inhalation RfC)

The weight of evidence from limited human data and more extensive animal data identify mild neurological impairment and possible developmental effects as potential health hazards from repeated inhalation exposure to xylenes. The animal inhalation exposure database contains no chronic toxicity studies, but there are a number of subchronic toxicity studies (of which several focused on neurological endpoints), a one-generation reproduction study in rats, and several developmental toxicity studies, some of which evaluated offspring for performance in neurobehavioral tests. Subchronic toxicity assays in animals have not found consistent evidence for other noncancer effects, such as changes in body weight or in hepatic, hematologic, or renal toxicity endpoints, following exposure to concentrations of xylenes as high as 800–1000 ppm for 6 hours per day, 5 days per week (e.g., Carpenter et al., 1975; Jenkins et al., 1970; Korsak et al., 1992, 1994).

Reversible symptoms of neurological impairment and irritation of the eyes and throat are well-known health hazards from acute inhalation exposure to xylenes and other aromatic solvents. In general, these acute effects are expected to involve reversible molecular interactions of the solvent itself (not metabolites) with membranes of the

affected tissues, including neuronal membranes, and are most pronounced at high exposure levels in excess of 1000 ppm. At lower concentrations, more subtle effects may occur. Human volunteers exposed under controlled conditions to xylenes concentrations in the range of 200–400 ppm for short time periods (15 minutes to 4 hours) have reported symptoms of irritation (e.g., watering eyes and sore throat) or neurological impairment (e.g., mild nausea, headache) (Carpenter et al., 1975; Gamberale et al., 1978).

In other studies involving single or multiple 4-hour exposures of human volunteers to 200 ppm xylenes, reversible effects on balance and reaction times have been reported (Laine et al., 1993; Savolainen and Linnavuo, 1979; Savolainen et al., 1984); however, other studies of 4-hour exposures to 200 ppm have not found impaired performance in tests of simple reaction time, short-term memory, and choice reaction time (Olson et al., 1985) or changes in visually evoked brain potentials (Seppäläinen et al., 1983) or electroencephalographic patterns (Seppäläinen et al., 1991). Impaired performance on tests of memory and reaction times was also reported for subjects exposed to 100 ppm xylenes for 4 hours (Dudek et al., 1990). The available controlled-exposure human studies indicate that concentrations around 100–200 ppm are close to the threshold level for short-term reversible neurological and irritation effects from xylenes.

The available human data alone do not provide adequate evidence for neurological impairment from repeated exposure to xylenes concentrations less than or equal to 200 ppm. Aside from the controlled-exposure studies reviewed above, most of the human data associating xylenes exposure to neurological impairment are case reports involving acute high-level exposures (800–10,000 ppm) (e.g., Goldie, 1960; Hipolito, 1980; Klaucke et al., 1982). Epidemiologic studies are restricted to a cross-sectional health evaluation study (Uchida et al., 1993) that reported increased prevalence of self-reported neurological symptoms and irritation, but no apparent changes in serum enzymes indicative of liver or kidney damage in a group of Chinese workers. The workers were from a boot manufacturing plant that used a xylene-containing glue and two other plants that used mixed xylenes as a solvent in wire production or printing. The measured time-weighted-average mean concentration of airborne xylenes in these workplaces was 21 (± 21) ppm. The study has several limitations, including a lack of reporting on the duration of exposure, co-exposure to other chemicals, no clear demonstration of relationships between response and dose or duration, and the inherent bias presented by self-reporting of symptoms.

Although the human evidence for persistent effects on the nervous system or other persistent effects from repeated inhalation exposure to xylenes is inadequate, results from animal studies more clearly identify potential persistent neurological impairment and possible developmental effects as potential health hazards from repeated inhalation exposure.

Overall results from rat studies described in Section I.B.2 provide evidence that repeated exposure to m-xylene at concentrations $\geq$ 100 ppm (6 hrs/day, 5 days/wk) may produce persistent changes in several neurologic endpoints in adult rats. Supporting evidence for potential persistent neurologic effects from xylenes includes reports of changes in indices of hearing loss in rats exposed to $\geq$ 800 ppm mixed xylenes for 14 hours per day for 6 weeks (Pryor et al., 1987) and in rats exposed to 1000 ppm mixed xylenes for 18 hours per day, 7 days per week, for 61 days (Nylén and Hagman, 1994).

There are no studies of the possible developmental toxicity of inhaled xylenes in humans, but there are a number of studies examining standard developmental toxicity endpoints and neurobehavioral endpoints in offspring of animals exposed to mixed xylenes or individual xylene isomers. Evidence for impaired neurological development in rat offspring following gestational exposure to inhaled xylenes is not

strong or consistent. Changes in neurobehavioral variables reported for offspring of animals exposed during gestation are restricted to impaired cognitive but not motor performance in the Morris water maze test in female but not male offspring of rats exposed to 500 ppm mixed xylenes for 6 hours per day on gestation days 7–20 (Hass et al., 1995, 1997) and decreased rotarod performance in offspring of rats exposed to 200 ppm "technical" xylenes for 6 hours per day on gestation days 6–20 (Hass and Jakobsen, 1993). Deficits in the water maze test were only observed in female rat offspring raised in standard housing and not in female rats raised in "enriched" housing with various toys (Hass et al., 1995).

Although decreased rotarod performance by offspring was observed in the study by Hass and Jakobsen (1993), it was not observed in the later study by the same group of investigators (Hass et al., 1995). The reported effect on rotarod performance in the earlier study was questioned by Hass et al. (1995) because the test was not conducted by experimenters who were blind to the exposure status of the rats. In addition, offspring of rats exposed to 800 or 1600 ppm p-xylene for 6 hours per day on gestation days 7–16 performed similarly to offspring of nonexposed rats in tests of central nervous system development: an acoustic startle response test on postnatal days 13, 17, 21, and 63 and a figure-8 maze activity test on postnatal days 22 and 65 (Rosen et al., 1986).

Several other inhalation developmental toxicity studies have examined standard developmental toxicity endpoints in rats (Litton Bionetics, 1978; Bio/dynamics Inc., 1983; Rosen et al., 1986; Ungváry et al., 1980; Ungváry and Tátrai, 1985), mice (Ungváry and Tátrai, 1985) and rabbits (Ungváry and Tátrai, 1985) following gestational exposure to xylenes. These studies have most clearly identified maternally toxic levels for decreased body weight gain in pregnant rats at concentrations greater than or equal to 700 ppm o-, p-, or m-xylene for 24 hours per day (Ungváry et al., 1980) or 1600 ppm p-xylene for 6 hours per day (Rosen et al., 1986) and for maternal death and abortions in pregnant rabbits exposed to 230 ppm (but not 115 ppm) mixed xylenes or p-xylene for 24 hours per day (Ungváry and Tátrai, 1985). In rats, effects on fetal skeletal and visceral malformations (such as cleft palate) and variations (such as retarded skeletal ossification or extra ribs) were reported at concentrations of up to 700 ppm o-, m-, or p-xylene for 24 hours per day (Ungváry et al., 1980) or 780 ppm mixed xylenes for 24 hours per day (Bio/dynamics Inc., 1983; Litton Bionetics, 1978; Ungváry and Tátrai, 1985). Likewise, effects on skeletal and visceral malformations and variations were reported in mice at concentrations of up to 230 ppm mixed xylenes (12 hrs/day in three 4-hr periods) or 115 ppm o-, p-, or m-xylene by the same protocol (Ungváry and Tátrai, 1985) or in rabbits exposed to 115 ppm mixed xylenes or o-, p-, or m-xylene for 24 hours per day (Ungváry and Tátrai, 1985).

Statistically significant increased incidences of fetuses with retarded skeletal ossification or extra ribs were reported in these studies, but the incidences were reported on an exposure-group basis in all but one of the studies. No litter-specific information was provided except in the Litton Bionetics (1978) study, which reported that, after adjustment for covariance with litter size, incidences of fetuses with delayed ossification in rats exposed to 400 ppm were no longer statistically significantly different from control values.

The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer concentrations of 350 or 700 ppm for 24 hours per day (Ungváry et al., 1980) or a mixed xylenes concentration of 780 ppm for 24 hours per day (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 230 ppm for 24 hours per day (Ungváry and Tátrai, 1985). These effects, although of concern, occurred at concentrations above those at which neurobehavioral effects were found in adult male rats following subchronic exposure (see Section I.B.2.).

Information regarding the potential reproductive toxicity of xylenes in humans is restricted to case-control studies reporting possible associations between occupational exposure to xylenes and other solvents and spontaneous abortions (e.g., Taskinen et al., 1986, 1994). However, these studies are of limited usefulness in assessing the potential reproductive toxicity of xylenes, because the numbers of cases of spontaneous abortions were small, and the women had been exposed to a number of chemicals.

Two reproductive toxicity studies in rats exposed to xylenes by inhalation are available (Bio/dynamics Inc., 1983; Nylén and Hagman, 1994). In a one-generation reproductive/developmental toxicity study (Bio/dynamics Inc., 1983), male and female CD rats were exposed to 0, 60, 250, or 500 ppm xylenes (technical grade xylene: 2.4% toluene, 12.8% ethylbenzene, 20.3% p-xylene, 44.2% m-xylene, 20.4% o-xylene) by inhalation for 6 hours per day, 5 days per week, for 131 days prior to mating, with exposure continued in the females during gestation days 1–20 and lactation days 5–20. Two additional 500-ppm groups used the same exposure protocol, except that only the F_0 males were exposed in one, and only the F_0 females were exposed in the other. The highest exposure level in this study, 500 ppm, was a NOAEL for reproductive performance in the parental generation. Likewise, a study of male Sprague-Dawley rats exposed to 0 or 1000 ppm xylene solvent for 18 hours per day, 7 days per week, for 61 days reported no differences between control and exposed rats in several testicular endpoints and fertility (Nylén and Hagman, 1994).

In summary, human data are suggestive of neurological effects and irritation of the eyes and respiratory tract following inhalation exposure to xylenes. Animal studies have demonstrated that neurological effects are the most sensitive effect of xylenes inhalation, with measurable effects in several neurobehavioral endpoints beginning at concentrations as low as 100 ppm following subchronic exposure (Gralewicz et al., 1995; Korsak et al., 1992, 1994; Nylén and Hagman, 1994; Pryor et al., 1987). At higher exposure levels, changes in body weight have been reported by some studies (Tátrai and Ungváry, 1980; Tátrai et al., 1981) but not by others (Carpenter et al., 1975; Jenkins et al., 1970; Ungváry, 1990). Similarly, high-level exposure to xylenes has resulted in changes in liver morphology, weight, and enzymatic functions (Tátrai and Ungváry, 1980; Tátrai et al., 1981; Ungváry, 1990). Gestational exposure of animals to xylenes has resulted in neurodevelopmental effects (Hass et al., 1995, 1997; Hass and Jakobsen, 1993) and other possible developmental effects (Ungváry et al., 1980; Ungváry and Tátrai, 1985), but only at levels above those at which neurobehavioral effects in adult male rats were reported. Finally, no reproductive effects were found in a one-generation reproductive/developmental study of male and female rats exposed to 500 ppm xylenes (Bio/dynamics, Inc., 1983) or in male rats exposed to 1000 ppm xylenes for 61 days (Nylén and Hagman, 1994).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

__I.B.5. Confidence in the Inhalation RfC

Study -- Medium
Database -- Medium
RfC -- Medium

Confidence in the principal study is medium, because the study was an examination of a critical effect of xylenes toxicity that also examined organ weights, body weights, and hematological parameters but was of subchronic duration, examined only one sex of a single species, and did not conduct histologic examination of the animals. Confidence in the database is medium; the database contains several subchronic studies as well as several developmental studies, developmental neurotoxocity studies, and a one-generation reproductive toxicity study. However, a two-generation reproduction study and chronic animal data are lacking. Medium confidence in the

RfC results.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

__I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document – U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2002. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***

Agency Consensus Date – 01/30/2003

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

Back to top

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 02/21/2003

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral exposure and inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/cu.m air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), *data are inadequate for an assessment of the carcinogenic potential* of xylenes. Adequate human data on the carcinogenicity of xylenes are not available, and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response. Evaluations of the genotoxic effects of xylenes have consistently given negative results.

Data on the carcinogenicity of xylenes following inhalation exposure are limited. A number of human occupational studies have suggested possible carcinogenic effects of chronic inhalation exposure to xylenes. However, in each case co-exposure to other chemicals was a major confounder, leading to an inability to adequately assess the potential effects of chronic exposure to xylenes. Animal data on the carcinogenicity of xylenes following inhalation exposure are not available.

Examinations of the carcinogenicity of xylenes following oral exposure in humans are not available. NTP (1986) conducted a 2-year oral cancer bioassay in male and female Fischer 344 rats and male and female B6C3F1 mice. Rats were exposed to 0, 250, or 500 mg/kg-day of mixed xylenes by gavage for 5 days per week for 103 weeks. No evidence of carcinogenesis was seen in male or female rats. Similarly, mice exposed to 0, 500, or 1000 mg/kg-day for 2 years did not show evidence of carcinogenic effects (NTP, 1986). However, a study by Maltoni et al. (1983, 1985) reported an increase in the overall number of malignant tumors in male and female rats treated by gavage with 0 or 500 mg/kg mixed xylenes for 4 days per week for 104 weeks. However, only total tumor incidence was reported; descriptions of target organs and tumor types were not included in the report. In the absence of additional information and because only one dose was used, the Maltoni et al. study does not provide sufficient evidence of the carcinogenicity of xylenes in animals.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

__II.A.2. Human Carcinogenicity Data

Inadequate.

Associations between occupational exposure to xylenes and increased risk of leukemia (Arp et al., 1983; Wilcosky et al., 1984), non-Hodgkin's lymphoma (Wilcosky et al., 1984), and cancer of the rectum (Gérin et al., 1998), colon (Gérin et al., 1998), or nervous system (Spirtas et al., 1991) have been reported. However, a number of limitations preclude the usefulness of these data, including small sample sizes, no quantified exposure concentrations, and/or concurrent exposures to other solvents.

__II.A.3. Animal Carcinogenicity Data

Inadequate.

In National Toxicology Program toxicology and carcinogenesis studies (NTP, 1986), groups of 50 male and 50 female Fischer 344/N rats and 50 male and 50 female B6C3F1 mice were administered mixed xylenes (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, 9.1% o-xylene) in corn oil by gavage at doses of 0, 250, or 500 mg/kg-day (rats) and 0, 500, or 1000 mg/kg-day (mice) for 5 days per week for 103 weeks. Necropsy and histologic examinations were performed on all animals.

In rats, no statistically significantly increased incidences of nonneoplastic or neoplastic lesions were found in exposed groups when compared with controls. A survival-adjusted increased incidence of interstitial cell tumors was found in the high-dose male rat group relative to controls, but this was not considered to be a treatment-related increase. The authors attributed the increase to high-dose male rats dying between weeks 62 and 92, noting that incidences for these tumors were comparable with controls during other time intervals and that the overall incidences were not statistically significantly different between control and exposed groups. In

mice, no statistically significantly increased incidences of nonneoplastic or neoplastic lesions were found in male or female exposed groups when compared with controls. NTP (1986) concluded that the study provided no evidence of carcinogenicity of xylenes in male or female F344/N rats or B6C3F1 mice.

Maltoni et al. (1983, 1985) exposed groups of 40 male and 40 female Sprague-Dawley rats to 500 mg/kg mixed xylenes (unspecified proportions) in olive oil orally by gavage 4–5 days per week for 104 weeks. The control groups of 50 males and 50 females were treated with olive oil only. Rats were kept under observation until spontaneous death; all rats died by 141 weeks. Percentages of mice that survived treatment were similar in controls and treated groups through 92 weeks (Maltoni et al., 1983), but survival data for later periods were not reported (Maltoni et al., 1985). For example, 50% and 65% of exposed males and females, respectively, survived at 92 weeks, compared with 58% and 66% of control males and females.

Only limited information regarding tumor incidences at specific tissue sites was provided with no information provided on nonneoplastic lesions or tumor pathology. Final (i.e., 141-week) tumor incidence data were reported only for rats with hemolymphoreticular neoplasias (thymomas, others, and total) and for rats with malignant tumors at any site (Maltoni et al., 1985). Incidences for thymomas were 1/34 and 0/36 in exposed males and females, compared with 0/45 and 0/49 in controls. Incidences of rats with other hemolymphoreticular neoplasias (not otherwise specified) were 4/34 and 3/36 in exposed males and females, compared with 3/45 and 1/45 in controls.[1] Fishers exact tests (performed by Syracuse Research Corporation) indicated no significant differences between groups in the incidences for hemolymphoreticular neoplasias (including the combined incidence for thymomas and "others").

The study authors also reported an increase in the total number of exposed rats with malignant tumors (of unspecified type): 14/38 and 22/40 for exposed males and females, compared with 11/45 and 10/49 for controls.[2] The exposed female total malignant tumor incidence is statistically significantly increased when compared with controls by the Fishers exact test. Because of the incomplete reporting of site-specific tumor incidence data and pathology, the study by Maltoni et al. (1983, 1985) is of limited use in evaluating the carcinogenicity of xylenes.

[1]Denominators are the number of rats reported to have been alive at 58 weeks when the first hemolymphoreticular neoplasia was observed.

[2]The denominators are the reported numbers of rats alive at 33 weeks when the first malignant tumor was observed.

__II.A.4. Supporting Data for Carcinogenicity

The genotoxicity of commercial xylenes and all three individual isomers has been studied and the results are, for the most part, negative (IARC, 1989). All studies cited in the GENE-TOX database are negative with the exception of one study for which no conclusion was drawn. Xylenes are not mutagenic in bacterial test systems with *Salmonella typhimurium* (Bos et al., 1981; Florin et al., 1980; NTP, 1986) and *Escherichia coli* (McCarroll et al., 1981) or in cultured mouse lymphoma cells (Litton Bionetics, 1978). Xylenes do not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (Anderson et al., 1990) or cultured human lymphocytes (Gerner-Smidt and Friedrich, 1978), chromosomal aberrations in rat bone marrow (Litton Bionetics, 1978), micronuclei in mouse bone marrow (Mohtashamipur et al., 1985), or sperm head abnormalities in rats (Washington et al., 1983). Technical grade xylenes, but not o- and m-xylene, are weakly mutagenic in *Drosophila* recessive lethal tests (Donner et al., 1980). No increase in the frequency of sister chromatid exchanges was observed in peripheral lymphocytes in individuals exposed to xylenes in an occupational setting (Haglund et al., 1980; Pap and Varga,

1987) or an experimental setting (Richer et al., 1993).

Back to top

_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

Back to top

_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

Back to top

_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document – U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2002. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date – 01/30/2003

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

Back to top

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 02/21/2003

_VI.A. Oral RfD References

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Back to top

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Back to top

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Back to top

_VII. Revision History

Substance Name -- Xylenes
CASRN -- 1330-20-7

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
07/01/1989	I.B.	Inhalation RfD now under review
07/01/1989	VI.	Bibliography on-line
03/01/1991	II.D.3.	Primary contact changed
03/01/1991	IV.F.1.	EPA contact changed
01/01/1992	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
08/01/1995	I.B.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this

		information.
12/10/1998	I., II.	This chemical is being reassessed under the IRIS Program.
02/21/2003	All	Revised RfD, RfC, Cancer assessment.

Back to top

_VIII. Synonyms

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 02/21/2003

108-38-3
1330-20-7
106-42-3
95-47-6
dimethylbenzene
1,2-dimethylbenzene
1,3-dimethylbenzene
1,4-dimethylbenzene
mixed xylenes
m-xylene
meta-xylene
o-xylene
ortho-xylene
p-xylene
para-xylene
xylenes

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe* PDF format (113 Pages, 498 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

* You will need Adobe Acrobat Reader, available as a free download, to view some of the files on this page. See EPA's PDF page to learn more about PDF, and for a link to the free Acrobat Reader.

Back to top
